

REMARKS/ARGUMENTS

I. Rejections of Claims 100-105, 107, 108, 111-123, and 129-143 under U.S.C. § 112, ¶ 1 (written description).

The Office Action rejects the above mentioned claims and asserts that the written description requirement is not satisfied with respect to the claims drawn to the genus of "mutated steroid hormone superfamily ligand binding domain". To the extent that the rejections may be applied to the amended claims, Applicants respectfully traverse.

The written description requirement for a claimed genus is satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, or by functional characteristics coupled with a known or disclosed correlation between function and structure. See the Office Action dated August 29, 2001. See also, Guidelines for Examination of Patent Applications Under the 3 U.S.C. 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001).

Applicants have provided relevant identifying characteristics of the claimed mutated steroid hormone superfamily ligand binding domain in the specification. Structurally, the non-mutated steroid hormone superfamily ligand binding domain is located at the carboxyl-terminal half of the receptor and consists of about 300 amino acids. (Spec., p. 2, ll. 21-23). The mutated ligand binding domain has small C-terminal alternations in amino acid sequence, including truncation, or deletion of carboxyl-terminal amino acids (Spec., p. 5, ll. 21-24). The chemical properties or the functional

characteristics of the mutated ligand binding domain includes its ability of distinguishing a steroid hormone receptor antagonist from a steroid hormone receptor agonist (Spec., p. 5, II. 13-15) and its binding ability only to a compound selected from the group consisting of non-natural ligands, anti-hormones and non-native ligands (Spec., p. 6, II. 26-30)

The specification also discloses a correlation between function and structure. For example, the small C-terminal alternations in amino acid sequence, including truncation, result in altered affinity and altered function of the ligand (Spec., p. 3, II.20-22). The C-terminal alternation causes a mutated ligand binding domain to distinguish a steroid hormone receptor antagonist from a steroid hormone receptor agonist (Spec., p. 5, II. 13-15)

Furthermore, Applicants present an example that a mutated progesterone receptor having a deletion of 42 or 54 amino acids from the C-terminus is capable of binding a natural antagonist of the non-mutated progesterone receptor. The example is representative of the claimed genus, since it shows that a mutated steroid receptor ligand binding domain (the mutated progesterone receptor ligand binding domain) having a alternation of C-terminal amino acids (a deletion of 42 or 54 C-terminal amino acids) binds only to a natural antagonist (RU 38486) of the non-mutated steroid receptor (the progesterone receptor). Applicants remind that one example can adequately support a genus. In re Herschler, 591 F.2d 693 (C.C.P.A., 1979) (disclosure of corticosteroid sufficient to support claims drawn to a physiologically active steroid).

In light of the foregoing, the specification adequately describes the claimed mutated steroid hormone superfamily ligand binding domain genus in such a way as to reasonably convey to one skilled in the relevant art that Applicants, at the time the application was filed, has possession of the claimed invention. Accordingly, Applicants respectfully request that the rejections be reconsidered and withdrawn.

II. Rejections of Claims 100-105, 107, 108, 111-123, and 129-143 under U.S.C. § 112, ¶ 2 (enablement).

A. "level of the expression of transgene in a transgenic animal".

The Office Action asserts that the above identified claims are rejected under 35 U.S.C. § 112, ¶ 2, for lack of enablement. The Office Action reasons that "it is unpredictable whether the transgene would be expressed at a high enough level so that it can be detected, and thereby, the expression [of the reporter gene] can be regulated" and that "one skilled in the art would not know how to use transgenic animals that simply comprise the transgene without actual mRNA or protein expression to practice the methods as claimed". To the extent the rejections may be applied to amended claims, Applicants respectfully traverses.

It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in the unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the

claimed genus possess the disclosed utility. In Re Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991).

Applicants disclose a method of determining the expression of a mutant steroid receptor using the well-known Western analysis (Example 12). Applicant further teaches a method of determining the transcriptional activity of the mutated steroid receptor and the expression of a reporter gene using the Western Analysis (Example 15). Since the Western analysis method is well known in the art, one of ordinary skill in the art would readily screen and determine which transgenic animal species possess the disclosed utility of regulating the expression of a desired protein or whether the expression of the reporter gene can be regulated.

It is unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened. In re Wands, 858 F.2d 731, 740 (Fed. Cir. 1988). Similarly, in the present application, it is unlikely that undue experimentation would be defined in terms of the number of transgenic animals that are not screened.

B. "mutated steroid hormone receptor superfamily ligand binding domain".

The Office Action asserts that the above identified claims are not enabling since "based on the disclosure of the specification, whether mutations of other kind would produce a receptor having the characteristics as claimed is unpredictable, and whether deleting same number of amino acids from C-terminal of other receptor in the steroid hormone receptor superfamily would produce a receptor having the characteristics as claimed is also unpredictable". To the extent the rejections may be applied to amended claims, Applicants respectfully traverses.

For reasons set forth in Section II (A) of this response, the relevant issue is whether the disclosure adequately guides the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. In re Vaeck, *supra*. Additionally, it is well settled that it would not require undue experimentation to practice the claimed invention when "there was considerable direction and guidance" in the specification, "all the methods needed to practice the claimed invention were well known", and working examples were provided in the disclosure. In re Wands, *supra*.

Applicants teach that the non-mutated steroid hormone superfamily ligand binding domain is located at the carboxyl-terminal half of the receptor and consists of about 300 amino acids. (Spec., p. 2, ll. 21-23). The mutated ligand binding domain has small C-terminal alternations in amino acid sequence, including truncation, or deletion of carboxyl-terminal amino acids. Applicants also teach methods of making the alternations in Example 7 and Example 9, methods of characterizing mutated steroid receptors in Example 11, methods of assaying the transcriptional activities of mutated receptors in presence of ligands in Examples 14 and 15. All the methods needed to practice Applicants' claimed invention are well known in the art. In addition, Applicants provide a working example in the disclosure, that is, the mutated progesterone receptor having a deletion of 54 or 42 carboxyl terminal amino acids and possessing the disclosed characteristics of binding to RU38486 and regulating the transcription activity of a reporter gene.

In sum, Applicants provide considerable direction and guidance in the disclosure that allow a skilled artisan to determine, without undue experimentation, which mutated steroid hormone superfamily ligand binding domain possess the disclosed

characteristics. In light of Vaeck and Wands, the disclosure is enabling with respect to the mutated steroid hormone receptor superfamily ligand binding domain.

C. "transgenic animals or long term expression".

The Office Action concedes that the specification is enabling for a method of regulating gene expression transiently *in vivo* by either a) introducing into a wild type animal a construct encoding a progesterone receptor with at least 42 amino acid deletion from C-terminal, and another construct comprising a progesterone receptor responsive element linked to a reporter gene; or b) administering a ligand that binds to said mutated receptor to said animal, or administering a ligand that binds to a mutated steroid receptor to a transgenic non-human animal, wherein said transgenic non-human animal expresses a reporter gene and a mutated steroid receptor, wherein expression of said receptor regulates the expression of the reporter gene by binding to the promoter of said reporter gene.

However, the Office Action asserts that the specification does not reasonably provide enablement for the method utilizing any transgenic animal or long term expression in any animal, and/or any mutated steroid hormone receptor that is capable of binding a ligand that is an antagonist of the natural occurring receptor. To the extent the rejections may be applied to amended claims, Applicants respectfully traverses.

Applicants have presented reasons that the specification is enabling with respect to transgenic animals and the mutated steroid hormone receptor genus in Sections II(A) and (B), which for sake of brevity are not repeated herein.

Turing to long term expression in an animal, Applicants teach that nucleic acid cassette can be introduced into cells by a variety of procedures, including transfection and transduction (Spec., p. 13, ll. 2-4, p. 17, ll. 22-23). "Transduction" is defined to the process of introducing recombinant virus into a cell by infecting the cell with a virus particle (P. 13, ll. 9-12). Transduction may introduce genetic materials into the chromosome of the targeted cell where it become a permanent component of the genetic materials of the cell. (P. 13, ll. 18-22). Additionally, it is known in the art that whether an exogenous genetic material becomes a part of chromosomes of a cell can be readily determined by a variety of methods including a Southern analysis. In light of the above, not only the transient expression, but also the long-term expression of the construct in an animal is enabling.

Finally, the fact that Office Action acknowledges the enablement of the transient expression of the construct *in vivo* means that the Office Action recognizes that Applicants provide adequate guidance to make and use transient *in vivo* expression in an animal of a reporter gene in presence of a ligand that binds to the mutated steroid receptor. The guidance includes methods of making the mutated receptor, introducing the genes into the animal *in vivo*, measuring the expression of the reporter gene, assaying the transcriptional activity of the mutated receptor, and determining which animal reach the regulated expression. One skilled artisan can readily appreciate that it requires no more guidance for the expression in a transgenic animal or the long term expression in an animal than for the transient expression. Applicants find no reason why the specification is enabling for the transient expression *in vivo* but not enabling for a transgenic animal or a long term expression in an animal.

In view of the foregoing, Applicants respectfully request that the rejections of the above identified claims be reconsidered and withdrawn.

III. Rejections of claims 118, 119, 136, 142 and 143 are rejected under 35 U.S.C. § 112, ¶ 2, for being indefinite.

Applicants amend claims 118, 119, 136, 142, 143 to meet the requirement of 35 U.S.C. § 112, ¶ 2. In particular, The term "transcription region" in claims 118 and 119 is replaced with the term "transactivation domain". The phrase "derived from" in claim 137 is replaced with the term "the ligand binding domain of". Finally, the term "regulated expression" of claims 142 and 143 is replaced with the term "the expression". Accordingly, Applicants respectfully request that the rejections be withdrawn.

IV. Rejections of claims 111, 139 and 141 are rejected under 35 U.S.C. § 112, ¶ 2, for being indefinite.

Applicants have amended claims 111, 139 and 141 to meet the requirement of 35 U.S.C. § 112, ¶ 2, and therefore respectfully request that the rejections be withdrawn.

In view of the foregoing, the claims pending in the application comply with the requirements of 35 U.S.C. § 112. A Notice of Allowance is, therefore, respectfully requested.

Respectfully submitted,
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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

100. ([Twice] Third Amended) A method of regulating expression of a desired protein or RNA in an animal, [said] the method comprising:

administering to [said] the animal a pharmacological dose of a ligand, wherein the ligand is an antagonist for a non-mutated receptor protein [which binds to a mutated steroid receptor superfamily ligand binding domain],

wherein [said] the animal contains:

(a) a first nucleic acid cassette comprising [which comprises a promoter transcriptionally linked to] a coding sequence of a molecular switch comprising a mutated receptor protein[coding sequence],

wherein [said] the mutated receptor protein [coding sequence comprises a nucleic acid sequence encoding a mutated receptor protein which regulates the transcription from a molecular switch promoter, and wherein said mutated receptor protein] comprises:

a DNA binding domain which binds [said molecular switch] a promoter transcriptionally linked to a target gene;

a [the] mutated steroid hormone receptor superfamily ligand binding domain[,] which is distinct from a naturally occurring ligand binding domain has an amino acid alternation in C-terminus and binds to the ligand;

a transactivation domain which causes transcription from [said molecular switch] the promoter when [said] the [mutated receptor protein] molecular switch is bound to [said molecular switch] the promoter and [to] the ligand [which is an antagonist for a non-mutated receptor protein]; and

(b) a second nucleic acid cassette comprising a nucleic acid encoding [the desired protein or RNA transcriptionally linked to said molecular switch promoter;] the target gene,

wherein administration of [said] the ligand regulates expression of [said] the desired protein or RNA from the target gene [in said animal].

101. (Amended) The method of claim 100, wherein the mutated steroid hormone superfamily receptor ligand binding domain is selected from the group consisting of estrogen, progesterone, androgen, Vitamin D, COUP-TF, cis-retinoic acid, Nurr-1, thyroid hormone, mineralocorticoid, glucocorticoid-alpha, glucocorticoid-beta, and orphan receptor ligand binding domains.

102. (Twice Amended) The method of claim 100, wherein the mutated receptor protein is [comprised of] a mutated progesterone receptor [with the native] and the DNA binding domain is [replaced with] a GAL-4 DNA binding domain.

103. (Twice Amended) The method of claim 100, wherein the nucleic acid encoding [said] the desired protein is transcribed to produce an mRNA molecule that is translated to produce the desired [a] protein after the animal is given the pharmacological [a] dose of [a ligand which binds to the mutated steroid hormone receptor superfamily ligand binding domain] the ligand.

104. (Amended) The method of claim 100, wherein the first nucleic acid cassette and the second nucleic acid cassette in [said] the animal are on separate plasmids.

105. (Amended) The method of claim 100, wherein the [mutated steroid receptor comprises] DNA binding domain is a natural DNA binding domain, a non-native DNA binding domain, or, a [or] modified DNA binding domain.

108. (Twice Amended) The method of claim 100, wherein the [said] animal is a mammal.

109. (Amended) The method of claim 107, wherein the [said] mammal is a human.

[111. (Amended) The method of claim 100, wherein the molecular switch is linked to a nucleic acid cassette thereby forming a cassette/molecular switch complex and said complex is positionally and sequentially oriented in a vector such that the nucleic acid in the cassette is transcribed and translated in said target animal.]

114. (Amended) The method of claim 100, wherein the mutated steroid hormone superfamily receptor ligand binding domain [is mutated to bind] binds to a compound selected from the group consisting of non-natural ligands, non-native hormones and anti-hormones.

115. (Amended) The method of claim 100, wherein [said] the DNA binding domain is a [replaced with a DNA binding domain selected from the group consisting of] GAL-4 DNA binding domain, a virus DNA binding domain, an insect DNA binding domain, or [and] a non-mammalian DNA binding domain.

116. (Amended) The method of claim 100, wherein [said] the transactivation domain is selected from the group consisting of VP-16, TAF-1, TAF-2, and TAU-2.

117 (Amended) The method of claim 116, wherein [said] the transactivation domain comprises a TAF-1 transactivation domain.

118 (Amended) The method of claim 100, wherein [said] the transactivation domain is a VP-16 transactivation domain [transcription region] and wherein [said] the DNA binding domain is a GAL-4 DNA binding domain.

119 (Amended) The method of claim 100, wherein [said] the transactivation domain is a TAF-1 transactivation domain [transcription region] and wherein [said] the DNA binding domain is a GAL-4 binding domain.

120 (Amended) The method of claim 100, wherein [said] the molecular switch is tissue specific.

121 (Amended) The method of claim 120, wherein the tissue specificity of [said] the molecular switch is controlled by [selection of] a tissue-specific transactivation domain.

123. (Twice Amended) The method of claim 100, wherein [said] mutated steroid receptor results from] the amino acid alternation is a deletion of carboxyl terminal amino acids in the mutated steroid hormone receptor superfamily ligand binding domain.

127. (Amended) The method of claim 100, wherein [said] the ligand is an endogenous ligand for [said] the mutated steroid hormone receptor.

129. (Twice Amended) The method of claim 100, wherein [said] the ligand is 11 beta-(4-dimethylaminophenyl)-17 beta-hydroxy-17 alpha-propinyl-4,9-estradiene-3-one.

131. (Amended) The method of claim 100, wherein [said] the ligand requires conversion to an active form in an end organ.

132. (Amended) The method of claim 100, wherein [said] the ligand has a side chain which increases or restricts solubility, membrane transfer or target organ accessibility.

133. (Twice Amended) The method of claim 101, wherein [said] the mutated steroid receptor superfamily ligand binding domain is a Vitamin D ligand binding domain.

134. (Twice Amended) The method of claim 133, wherein [said] the mutated receptor is activated when bound by the ligand 24,25-dihydroxy-Vitamin D.

135. (Twice Amended) A method of regulating an expression from a desired protein or RNA in an animal comprising:

administering to the animal a pharmacological dose of a ligand that activates a molecular switch [protein] encoded by a first expression cassette comprised in the animal, wherein the activation of the molecular switch [protein] results in the expression of the desired protein or RNA from a second expression cassette comprised in the animal, wherein the molecular switch [promoter] comprises a mutated steroid hormone superfamily receptor ligand binding domain which is activated by the [administered] ligand [but not by] a native ligand for a corresponding wild type steroid hormone superfamily receptor ligand binding domain.

136. (Amended) The method of claim 135, wherein the mutated steroid hormone superfamily receptor ligand binding domain is [derived from] the ligand binding domain of a steroid hormone superfamily receptor selected from the group consisting of: estrogen; progesterone; glucocorticoid- α ; glucocorticoid- β ; mineralcorticoid; androgen; thyroid hormone; retinoic acid; retinoid X; Vitamin D; COUP-TF; ecdysone; Nurr-1 and orphan receptors.

137. (Amended) The method of claim 136, wherein the mutated steroid hormone superfamily receptor ligand binding domain is a mutated progesterone ligand binding domain and the ligand is an anti-progestin.

140. (Amended) The method of claim 135, wherein the molecular switch comprises a mutated steroid hormone receptor superfamily ligand binding domain operably attached to a DNA binding domain selected from the group consisting of: a GAL-4 DNA binding domain; a viral DNA binding domain; an insect DNA binding domain; and a non-mammalian DNA binding domain.

143. (Amended) The method of claim 135, wherein the [regulated] expression is up-regulated [ion].

144. (Amended) The method of claim 135, wherein the [regulated] expression is down-regulated [ion].